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# Transplantation of the Liver

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# ***Past, Present, and Future of Liver Transplantation***

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The ultimate therapeutic step in the treatment of hepatic disease is the provision of a new liver, with or without removal of the affected native organ. As of this writing, nearly 3,000 liver transplants have been performed in the United States alone. Probably another 1,000 have been performed in other countries.

## **The Past**

Two different approaches to liver transplantation have been utilized. The first consists of insertion of an extra liver (auxiliary liver transplantation) at an ectopic location. This approach leaves the recipient's diseased liver alone. The alternative approach to auxiliary hepatic transplantation is orthotopic liver transplantation. With this operation, the diseased liver is removed, creating a space into which the allograft is transplanted, with as normal an anatomic reconstruction as possible based upon the specific liver pathology and the prior surgical history of the recipient.

## **Auxiliary Liver Transplantation**

The first attempts at whole liver grafting were auxiliary grafts and were carried out by Welch et al (1,2). The use of auxiliary grafts for the treatment of benign hepatic disease had an initial attractiveness because it was thought that the sacrifice of the remaining function of the failing liver could be avoided and would provide some reserve in the event of poor performance on the part of the liver graft. Unfortunately, the results obtained with auxiliary liver transplantation have been consistently inferior to those obtained with orthotopic liver replacement.

For an auxiliary graft, the arterial supply is derived from either the aorta or the iliac artery, whereas venous inflow is provided by either the distal iliac vein or the inferior vena cava to the graft's portal vein. The hepatic venous outflow is into either the proximal iliac vein or the inferior vena cava. Initially auxiliary

grafts produce bile, but after several days they gradually cease to function and undergo progressive atrophy. Essentially all attempts at transplanting an extra liver (auxiliary transplantation) without removal of the diseased native organ have been disappointing (3). As a result, it is generally believed that auxiliary transplantation, if used at all, should be reserved for patients with acute hepatic disease for whom the objective is temporary life support, during which time recovery of the native liver may occur. In such cases, the extra liver is being used as a temporary support organ and can be removed once the recipient's native liver begins to function. Auxiliary liver transplantation might also be considered for those few patients who have had extensive prior abdominal surgery in the right upper quadrant and for whom orthotopic liver transplantation would otherwise be either very difficult or impossible to accomplish.

The major drawback of auxiliary grafts is that they atrophy and fail to function with time. That this occurs should not be particularly surprising, however. As long ago as 1877, Eck described the procedure of portacaval shunting (4) and 16 years later, Hahn et al (5) extended this study by reporting the untoward effects of this procedure. These included weight loss, encephalopathy, and liver atrophy. It took another 75 years, however, before it was realized that the hepatic atrophy produced by portacaval shunting occurs very rapidly, being 90% complete within 3–4 days. Paradoxically, the mitotic index and the rate of thymidine incorporation increase to a level three to four times greater than the preoperative level within the liver undergoing atrophy. Subsequently it was noted that if the splanchnic venous blood flow is restored to the liver, the liver atrophy experienced after portacaval shunting does not occur (6). Based upon this observation, it was suggested that portal venous blood might contain one or more hepatotrophic factors and that the diversion of these factors away from the liver with portacaval shunting is responsible for the hepatic atrophy experienced afterward. A contrasting hypothesis, championed by Mann (7), is that the hepatic atrophy or lack of atrophy occurring after portacaval shunting is blood flow dependent. Several early studies by Child et al (8), using portacaval transposition as the experimental model, have been interpreted by some as favoring the Mann hypothesis. Specifically, these studies suggest that by replacing the diverted splanchnic venous blood with an inflow to the portal vein from the inferior vena cava, most of the adverse effects of portacaval shunting could be avoided.

As a result of this observation, the fate of liver tissue given different types of portal venous inflow has been investigated. In one such model (9), splanchnic venous blood is provided to one segment of the liver via the portal vein, whereas the other segments are supplied with blood from the inferior vena cava. The segments receiving flow from the vena cava invariably atrophy. Moreover, the atrophy cannot be prevented by arterializing the disadvantaged segment. Another model, which has been used to evaluate the importance of portal venous blood for the maintenance of the hepatic mass, is the so-called double liver. In this preparation, blood returning from the pancreas, duodenum, and stomach passes to one portion of the liver, while the other half of the liver is perfused with venous blood returning from the small intestine. The liver segment perfused with blood from the upper abdominal viscera remains normal (10). In contrast, the liver perfused with intestinal venous blood undergoes progressive atrophy.

The role of endogenous insulin as a putative hepatotrophic factor responsible for the maintenance of hepatic volume was suggested when it was found

that liver segments atrophy if either a total pancreatectomy is performed or alloxan diabetes has been produced (11–13). These same experiments also demonstrated that nonpancreatic substances present in portal venous blood also contribute, at least in part, to the hepatotropic effect of splanchnic venous blood, as the atrophy produced in such models is less than that experienced with portacaval shunting. These experiments also provide a rational reason for the consistently poorer results obtained with liver transplantation using auxiliary grafting techniques compared to those obtained with orthotopic grafting procedures.

## Orthotopic Transplantation

Since the beginning of the cyclosporine era, more than 2,000 patients have had orthotopic liver transplants. The first such attempts reported were by Cannon (14). Subsequently, orthotopic liver transplantation was developed principally by Starzl and by Calne (15–17). The technical problems associated with orthotopic liver transplantation and the histopathologic features of liver rejection were originally studied in dogs (15–18). Using azathioprine and antilymphocyte serum (ALS) as the immunosuppressive agents, long-term survival of orthotopic liver transplants in dogs was reported by Starzl and others (19–25).

Subsequently, it was noted that the rejection experienced by orthotopic liver homografts in pigs was relatively mild compared with that experienced by livers transplanted into dogs (26). This observation provided an important impetus for human liver transplantation.

Orthotopic liver transplantation in a human was first attempted by Starzl in 1963 (27). The first extended survival (13 months) was achieved in 1967 (28,29). Initially, candidacy for this operation was restricted to individuals with hepatic malignancy who were less than 55 years old, free of extrahepatic infection, and free of extrahepatic malignancy. This was because transplantation for nonneoplastic disease was considered unjustifiable. It became acceptable to some only after considerable social and vocational invalidism had occurred as a result of hepatic encephalopathy, variceal hemorrhage, hepatorenal syndrome, intractable ascites, and a wide variety of other complications of hepatic disease (30). As a result, for many years, orthotopic liver transplantation was utilized only as a desperate attempt to rescue patients who were obviously dying. Unfortunately, deterioration frequently occurred either during evaluation for the procedure or during the time it took to identify an appropriate donor organ in many early cases. Once initiated, hepatic decompensation in patients with well-advanced chronic liver disease is rapid and leads to coma, anuria, gastrointestinal bleeding, multiple infections, and, ultimately, death unless liver transplantation can be accomplished. Complicating the course of these early cases further was the fact that many of them required ventilatory support and renal dialysis both before and after successful liver transplantation.

With continued experience, it became clear that liver transplantation is technically easy for some hepatic diseases and exceptionally difficult for others. Whatever the underlying hepatic disease, however, individuals with prior adhesion-forming operations, particularly those in the upper abdomen, have an increased perioperative mortality, especially if the porta hepatis has been dis-

**Table 1.1** Indications for Orthotopic Liver Transplantation

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|  |                                       |
|--|---------------------------------------|
| I. Chronic Advanced Liver Disease  |                                       |
| Predominantly cholestatic diseases   | Predominantly hepatocellular diseases |
| Primary biliary cirrhosis  | Chronic virus-induced liver disease   |
| Primary sclerosing cholangitis   | Chronic drug-induced liver disease    |
| Biliary atresia  | Alcoholic liver disease               |
| Familial cholestatic syndromes   | Autoimmune liver disease              |
| Vascular disease   |                                       |
| Budd-Chiari syndrome   |                                       |
| II. Hepatic Malignancies That Are Not Otherwise Resectable                             |                                       |
| Hepatoma   |                                       |
| Cholangiolar carcinoma   |                                       |
| Unusual nonhepatocellular or bile duct tumors that arise within the hepatic parenchyma |                                       |
| Isolated hepatic metastases  |                                       |
| Carcinoid  |                                       |
| Pancreatic islet cell tumor  |                                       |
| Others   |                                       |
| III. Fulminant Hepatic Failure   |                                       |
| Viral hepatitis  |                                       |
| A, B, B+, NANB   |                                       |
| EBV, other   |                                       |
| Drug-induced liver disease   |                                       |
| Halothane  |                                       |
| Gold toxicity  |                                       |
| Disulfiram   |                                       |
| Others   |                                       |
| Metabolic liver disease  |                                       |
| Wilson's disease   |                                       |
| Reyes' syndrome  |                                       |
| Organic acidurias  |                                       |
| IV. Metabolic Liver Disease  |                                       |
| Alpha-1-antitrypsin deficiency   |                                       |
| Wilson's disease   |                                       |
| Homozygous type II hyperlipoproteinemia  |                                       |
| Crigler-Najjar syndrome type I   |                                       |
| Protoporphyrria  |                                       |
| Some urea cycle deficiencies   |                                       |
| Glycogen storage diseases types I and IV   |                                       |
| Tyrosinemia  |                                       |

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sected for either a portal diversion or a biliary tract reconstructive procedure (31).

## The Present

The principal indications for liver transplantation are shown in Tables 1.1 and 1.2. The disease indications in pediatric patients (individuals under 18 years of age) are different from those in adults. In children, biliary atresia is the leading indication; in adults, it is postnecrotic cirrhosis. Other indications in adults include primary biliary cirrhosis, sclerosing cholangitis, and a large number of metabolic liver diseases.

A finding in 10% of early operations that often resulted in operative death was either a thrombosed or a hypoplastic portal vein. As a result of this ex-

**Table 1.2** Clinical and Biochemical Indications for Liver Transplantation Candidacy

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|   |
|---|
| I. Acute Liver Failure                            |
| Bilirubin >20 mg/dL                               |
| Prothrombin time >30 seconds above control values |
| Progressive encephalopathy of at least grade 3    |
| II. Chronic Liver Disease                         |
| A. Cholestatic liver disease                      |
| Bilirubin >12.5 mg/dL                             |
| Intractable pruritus                              |
| Intractable bone disease                          |
| B. Hepatocellular liver disease                   |
| Albumin <2.5 g/dL                                 |
| Hepatic encephalopathy                            |
| Protime >5 seconds above control values           |
| C. Factors common to both types of liver disease  |
| Hepatorenal syndrome                              |
| Recurrent spontaneous bacterial peritonitis       |
| Intractable ascites                               |
| Recurrent episodes of biliary sepsis              |
| Development of a hepatoma                         |

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perience, all potential liver transplant candidates currently are studied with ultrasonography to define the status of their portal vein preoperatively. Whenever the results are either equivocal or consistent with absence of the portal vein, either portal venography as part of a superior mesenteric arteriographic study or a nuclear magnetic resonance study is obtained to visualize the portal vein. This experience relative to the status of the portal vein, as well as others, has led us to develop a formal pretransplant evaluation for all liver transplant candidates seen at the University of Pittsburgh.

This evaluation has six goals: 1) confirmation of the specific hepatic disease diagnosis; 2) documentation of the severity of the liver disease; 3) measurement of the recipient's intellectual and psychiatric status; 4) assessment of abnormalities of extrahepatic organ systems that might adversely affect transplantation; 5) determination of whether liver replacement is anatomically possible; and finally, 6) assessment of whether procedures or therapies other than transplantation may be possible (31,32).

Because livers affected by hepatocellular disease are quite small, a donor with a smaller liver and therefore of smaller stature—usually 10 kg less than the recipient—is usually sought. Because of the combined effects of coagulopathy and portal hypertension in such cases, hemostasis is often difficult to obtain until the hypertensive portal venous system is decompressed, either through the liver graft or via a portal systemic bypass system. Once the new liver is in place, however, improved coagulation is to be expected if a well-preserved donor liver has been engrafted.

The transplant procedure may require many units of blood in patients with severe portal hypertension. Adhesions present from previous abdominal operations, other than portal systemic shunts, often create particularly fragile collaterals that tend to bleed profusely. If a surgically created portacaval shunt exists, the anastomosis must be taken down to revascularize the graft adequately. In such cases, the residual portal vein is frequently sclerotic and fragile,

and may be difficult to use. When prior portal venous shunting has been accomplished with a functioning mesocaval shunt, the shunt must be closed to prevent a "steal" syndrome that would otherwise deprive the liver graft of its portal venous blood supply. In most cases, however, mesocaval shunts prohibit transplantation as a result of retrograde portal venous thrombosis.

Transplantation for hepatitis B-induced liver disease has been and continues to be a clinical problem. The antigen titer in the few patients who have been studied has been reduced only temporarily after the operation, suggesting that the excised liver is the principal, but not the sole, reservoir for the virus in the body (3). Complete clearing of the virus perioperatively has not been achieved despite treatment with large quantities of hyperimmune globulin given intraoperatively in the immediate postoperative period, as well as 1 month after transplantation. A course of preoperative immunization with hepatitis B surface antigen (HB<sub>s</sub>Ag) vaccine to stimulate an antibody response before transplantation and subsequent immunosuppression have failed to result in either viral clearance or antibody production in HB<sub>s</sub>Ag-positive patients who have been transplanted.

These observations highlight the fact that the risks to medical personnel as a result of hepatitis B virus (HBV), non-A, non-B hepatitis (NANB) and human immunodeficiency virus (HIV) infections in recipients and donors are substantial. A program to immunize prospectively all staff involved in organ transplantation and to treat staff members after overt exposure with hyperimmune globulin should be mandatory in all transplant programs.

### **Specific Current Indications for Liver Transplantation**

#### **Biliary Atresia**

The prevalence of biliary atresia has been estimated to be between 1 in 7,000 and 1 in 13,000 live births. With approximately 3.7 million births annually in the United States, the number of new cases of biliary atresia per year should be between 400 and 500 (34). Most, but not all, of these individuals should be candidates for liver transplantation. The exceptions are those who have severe associated anomalies of other organ systems that prevent a meaningful life or prohibit transplantation for anatomic reasons; such conditions are estimated to occur in about 15% of these cases.

Children with biliary atresia need to be evaluated very carefully, as some of them have unexpected intra-abdominal venous and intestinal anomalies that prohibit the performance of an otherwise uncomplicated liver transplant (35,36). The most serious of these anomalies are an absent inferior vena cava, a preduodenal portal vein, a hypoplastic portal vein, hepatic arteries that are unsuitable for arterial reconstruction, and an absent retrohepatic inferior vena cava with situs inversus.

Because of recurrent episodes of cholangitis after a standard porticoenterostomy (Kasai procedure), an increasing number of children with biliary atresia have had multiple abdominal operations, particularly diverting jejunostomies. These often require later closure because of bleeding or stomal ulceration. The net result of such additional surgery has been that liver transplantation becomes increasingly difficult because of the highly vascular adhesions that are present in the hilar area in such cases.

## Hepatic Malignancy

When clinical liver transplantation was originally performed, individuals with primary hepatic neoplasms that could not be removed by conventional operative procedures were thought to be ideal candidates for liver transplantation. The prognosis for all such patients without transplantation was predictable: death within 6 months. Moreover, such candidates generally were in good physical condition and did not deteriorate while waiting for a donor organ. More importantly, portal hypertension seldom was severe in such cases. Finally, because livers filled with tumor are either normal in size or, more usually, enlarged, the technical demands of the transplantation procedure in such patients tend to be simple in comparison to those in individuals with advanced cirrhosis.

Unfortunately, the frequency of recurrent tumor after transplantation, as well as the recognition that immunosuppression, at least theoretically, accelerates metastatic growth, has dampened the initial enthusiasm for this procedure for this indication (18,30,35-37). Eighty-five percent of the recipients transplanted for this indication who have lived long enough for occult residual tumor to be evident have developed metastases. Moreover, recurrent disease is the principal cause of death in such recipients. The situation is even worse for those with cholangiocarcinoma. All such recipients have died of recurrent cholangiocarcinoma, usually less than a year after transplantation.

Categorical exclusion of tumor cases in the future, based upon this less than ideal experience with hepatic malignancy, should not be the rule, however. Primary hepatocellular carcinomas found incidentally in organs removed for cirrhosis have been cured as a result of resection.

## Postnecrotic Cirrhosis

Individuals with postnecrotic cirrhosis due to viral, autoimmune, or cryptogenic mechanisms are candidates for liver transplantation if they have any of the many complications that presage death in individuals with advanced liver disease (spontaneous bacterial peritonitis, hepatorenal syndrome, recurrent variceal bleeding), or if they have recurrent episodes of hepatic encephalopathy or advanced synthetic dysfunction characterized by hypoalbuminemia and coagulopathy. In general, these cases are difficult because of the combination of intense portal hypertension and coagulopathy. Nonetheless, as a group, they represent one-third or more of all current adult liver transplant cases.

## Alpha-1-Antitrypsin Deficiency

The issues of case selection and surgical technique for this metabolic liver disease are the same as those for postnecrotic cirrhosis, except that care should be taken to perform the transplant prior to the development of irreversible lung disease. After a successful operation, the protease inhibitor phenotype of the recipient converts to that of the donor, and depressed serum alpha-1-antitrypsin levels become normal. Whether lung disease will or will not develop in such cases following liver transplantation is not known, but this is thought to be unlikely.



## Other Metabolic Diseases of the Liver

A metabolic cure following liver transplantation has either been proven or presumed in children with types I and IV glycogen storage disease, tyrosinemia, and Wilson's disease (38-42). Most, but not all, of the characteristic perturbations of these metabolic disorders are corrected after liver transplantation (31,38-42).

## Alcoholic Liver Disease

Because alcoholics abuse a variety of organs, disease of the lungs and a variety of other organs, particularly the brain, is common in this population. Following successful transplantation, noncompliance and recidivism can be problems. Nevertheless, alcoholics have been transplanted, and some have experienced prolonged subsequent periods of sobriety. A reasonable period of alcohol abstinence prior to liver transplantation appears reasonable but is not essential. Such a requirement would certainly reduce the alcoholic candidacy list, either by producing a patient who is too well to be legitimately considered for transplantation or by documenting the patient's inability to maintain abstinence and comply with medical therapies following transplantation. Those few alcoholics who would adhere to a rehabilitation program and yet fail to regain adequate hepatic function clearly should be offered transplantation. Despite the many potential social and political issues relative to the use of liver transplantation for alcoholic cirrhosis, this indication can be expected to become a more frequent reason for liver transplantation in the future.

## Primary Biliary Cirrhosis

Transplantation for primary biliary cirrhosis is technically easier to perform than it is for any other hepatic disease. In this disease, the liver is either normal in size or enlarged, venous collaterals are not excessive, and occlusion of the recipient portal vein and vena cava during the anhepatic phase of the procedure is well tolerated. Recurrence of primary biliary cirrhosis after successful transplantation has been described but is not well accepted generally (43,44). The identification of this untoward consequence of transplantation may be difficult, if not impossible, until more is known about the pathophysiologic mechanisms of the primary disease. For the immediate future, primary biliary cirrhosis remains a major indication for liver transplantation.

## Primary Sclerosing Cholangitis

The indications for liver transplantation for primary sclerosing cholangitis are identical to those for primary biliary cirrhosis, except that many of these patients have had prior biliary tract surgical procedures, which make the recipient hepatectomy technically more difficult. Whether the original disease recurs in the allograft liver is currently uncertain. Moreover, the presence of associated inflammatory bowel disease (especially ulcerative colitis) may enhance this risk. Should quiescent ulcerative colitis be present, the question of whether or not elective colectomy should be performed to prevent disease recurrence in the allograft, and possibly cancer of the colon, in an individual who will require

**Table 1.3** Contraindications to Liver Transplantation

- 
- |     |   |
|-----|---|
| I.  | Absolute Contraindications  |
|     | A. Active sepsis outside the hepatobiliary tree   |
|     | B. Metastatic hepatobiliary malignancy  |
|     | C. Advanced cardiopulmonary disease   |
|     | D. AIDS   |
| II. | Relative Contraindications  |
|     | A. Advanced chronic renal disease   |
|     | B. Age greater than 60 years  |
|     | C. Portal vein thrombosis   |
|     | D. Cholangiolar carcinoma   |
|     | E. Hypoxemia with intrapulmonary right-to-left shunts   |
|     | F. Hepatitis B s antigen (HB <sub>s</sub> Ag) and hepatitis B e antigen (HB <sub>e</sub> Ag) positivity |
|     | G. Prior portacaval shunting procedure  |
|     | H. Prior complex hepatobiliary surgery  |
|     | I. HIV positivity without clinical acquired immune deficiency syndrome (AIDS)                           |
- 

long-term immunosuppression is important. Currently there are no data available to answer this question. However, the attitude of gastroenterologists and surgeons toward these particular issues has become more conservative, as most patients experience a lessening of their ulcerative colitis symptoms following liver transplantation, presumably as a result of the associated immunosuppression.

### Secondary Biliary Cirrhosis

The initiating event in patients with this disease has usually been incomplete biliary tract obstruction resulting from a series of unsuccessful attempts at earlier biliary tract reconstruction following one of several complicated biliary tract surgeries. If such patients are accepted as transplant candidates, the technical problems experienced by the surgeons during the procedure can be enormous. These arise both as a result of the altered anatomy and as a result of the numerous adhesions and the portal hypertension that are present. The biliary sepsis present in most such cases also enhances the risk.

### Budd-Chiari Syndrome

The fact that portal-systemic diversion by decompressing the liver improves hepatic function in some cases and avoids transplantation in some patients with the Budd-Chiari syndrome should not be forgotten. Thus many patients with the Budd-Chiari syndrome referred for transplantation will have had a prior side-to-side portacaval shunt. In such cases, the shunt has to be taken down at the time of transplantation. This can be very difficult and usually requires a portal vein graft.

### Contraindications to Liver Transplantation

The current list of contraindications to liver transplantation is shown in Table 1.3. Although only some of these contraindications are absolute, any of them

may be very serious. For example, preexisting systemic or local infections create highly unfavorable conditions, as do diseases of organs other than the liver, such as coexisting severe heart disease or a history of sociopathic behavior such as alcoholism or drug abuse.

Portal-systemic shunts are still being used to control variceal bleeding, but they are being recommended far less frequently than before, because the results of randomized clinical trials with shunts have not demonstrated a statistically significant increase in the survival of patients after portacaval shunting compared to the survival of those without this operation. Worse yet, the outcome after portacaval shunting is a decrease in mortality due to gastrointestinal hemorrhage, which is replaced by a higher death rate due to hepatic failure and/or disability due to hepatic encephalopathy. As a consequence, alternative methods (such as sclerotherapy and transhepatic embolization of the left gastric vein) to control variceal bleeding nonoperatively without changing the preexisting portal venous blood flow patterns have achieved increasing acceptance (45-49).

In all side-to-side shunts, the blood returning from the splanchnic bed is diverted around the liver. In addition, a variable amount of blood from the liver passes into the systemic venous circulation as a result of retrograde drainage (a steal phenomenon). Mesocaval H-graft procedures are no exception. In addition, the prostheses used in these procedures are associated with a high rate of late thrombosis that often propagates to involve the portal vein (48-49). Selective shunts are technically more difficult and demanding than the more conventional diverting shunts. Yet, if they can be accomplished, a distal splenorenal procedure can effectively decompress esophageal varices while maintaining hepatopetal portal venous flow. Thus, selective shunts are preferred to other techniques if a shunt procedure is necessary before liver transplantation.

## Organ Procurement and Preservation

In most transplantation centers in the United States, the criterion of brain death based on the concept of irreversible brain injury has been accepted. Under these conditions and with an ideal cadaveric donor, the interval of normothermic, ischemic injury is reduced essentially to zero. Fortunately, public acceptance of these conditions of organ removal has been widespread. Advances have also been made in the field of multiple organ harvesting. Usually the donor operation is done through a complete midline incision from the suprasternal notch to the pubis, which includes splitting the sternum. The aorta is dissected for cross-clamping at a level that will allow intra-aortic infusion of cold fluids to pass into all of the organs to be harvested. When the liver is one of the organs to be removed, dissection of the liver hilum begins only after the liver has been infused with cold fluid through both the aorta and the portal vein. This technique requires a stable cardiovascular situation (50,51).

An alternative procedure, which can be done more swiftly in unstable donors or those experiencing cardiac arrest, is the "fast method." With this method, a clamp is placed on the aorta near the diaphragm and cold solutions are infused rapidly, entering the liver both through the normal celiac axis route and through the portal vein after passing through the splanchnic viscera.

In removing a liver for transplantation, there are two essential steps. The

first is to incise the restraining ligaments that bind the organ to the diaphragm and body wall. The second is to skeletonize the vessels and bile duct that are to be anastomosed to the companion structures in the recipient.

Donor cardiovascular instability, a need for excessive vasopressor support, an excessive period (several days) between initial injury and the pronouncement of brain death, or deterioration of renal function suggest poor perfusion of the donor kidneys and liver and make the donor organs less than ideal as allografts (52-55). The most common explanations for poor graft function, however, are inadequate preservation or preexisting hepatic disease. Intelligent screening of all prospective donors and the elimination of those whose physiologic situation jeopardizes organ function are crucial to the maintenance of a transplant program.

Assuming that donor selection is appropriate, the surgical removal of a good donor organ for transplantation depends upon 1) performing a technically perfect operation, including recognition of any of the numerous anomalies of the hepatic arterial supply; 2) avoiding warm ischemia; and 3) minimizing cold ischemia. The first of these requirements is dependent on the knowledge and skill of the surgeon. The second is also surgeon dependent and can be met by avoiding occlusion of the blood supply during the dissection. The third calls for careful timing of the donor and recipient operations, which often take place across great distances. After the donor organ has been recovered, the distal aorta, iliac arteries, vena cava, and iliac veins of the donor should be removed and preserved in a balanced electrolyte solution for possible use as vascular grafts in the recipient, should they be required (51).

### **Tissue Matching and Liver Transplantation**

Waiting for a good match at the A, B, and DR loci of the major histocompatibility complex is currently not practical and probably will never be practical for liver transplantation because of the precarious medical condition of most liver transplantation recipients prior to surgery. It is of interest that hepatic transplantation has been performed by both the Starzl group and the Cambridge-King's College team despite a positive cytotoxic cross-match (52-57). Hyperacute rejection of the grafted liver in such cases has either not been seen or is markedly reduced in severity compared to that of renal grafts. In animal models of liver transplantation, in which the recipient has preformed heterospecific cytotoxic humoral antibodies, antibody-initiated rejection of the liver has been reported, but it occurs at a much slower rate than it does in the kidney (53-57); similarly, the mechanisms responsible for graft destruction in ABO-incompatible liver transplants are not well understood, but include graft-versus-host disease as well as allograft rejection. The reasons such grafts can be performed without hyperacute rejection remain to be explained.

### **Recipient Preparation and the Transplant Procedure**

Paracentesis and/or thoracentesis may be required before general anesthesia can be contemplated in a liver transplant recipient. Transfusions of blood or albumin are often useful for the correction of blood volume or other fluid space

abnormalities. If fresh whole blood, fresh frozen plasma, or platelets are given, improvement in the preoperative coagulation status of the recipient is usually possible.

A bilateral subcostal incision is used, with an upper midline extension through the xiphoid process. If removal of the liver is difficult, the incision can be extended into the right seventh intercostal space. This latter incision is required if the recipient's original liver is small. In such cases, special techniques are often required to construct adequate recipient vena caval cuffs for anastomoses with the donor organ (58,59). The suprahepatic and infrahepatic vena caval anastomoses are performed first. This is followed by reconstruction of the portal vein. At a convenient time, air and the potassium-rich organ preservation fluid within the graft must be washed out. Portal blood flow is usually restored first. After checking for major anastomotic leaks, the hepatic arterial anastomosis is performed, followed by the biliary reconstruction.

### **Portal Venous Bypass and Liver Transplantation**

Usually portal and vena caval occlusion can be tolerated during the 45- to 90-minute anhepatic phase of the operation, despite major reductions in the cardiac output and the obligate hypotension that follows portal vein and vena cava clamping (60). The ease with which these vessels can be occluded has been shown to be dependent upon the degree of collateral circulation that has developed and that allows venous return to occur despite such large vessel occlusion. If severe hypotension occurs with cross-clamping, a bypass system should be used (55,59).

The fact that most patients do well with portal and inferior vena caval cross-clamping has created an impression in the minds of some surgeons that this practice is entirely safe. When portal cross-clamping is performed without a bypass, the intestine becomes progressively more boggy and edematous and tends to weep into the peritoneal cavity. Subsequently, the recipient often suffers from third space fluid losses, peritoneal contamination with the development of subsequent enteric bacterial and fungal infections, and postoperative renal dysfunction. The extent to which any one of these complex physiologic events contributes to the high perioperative mortality of liver transplantation patients has not been delineated until recently. With the routine use of a heparin-free venous bypass system, the transplant operation can be performed under controlled circumstances and the rate of postoperative fungal and bacterial infection can be reduced dramatically. As a result, patient survival is increased. The veno-venous bypass has changed the technical strategy of liver transplantation in several other important ways. In the past, when time was a critical factor during the anhepatic phase, it was often impossible to perform meticulous hemostasis. When the veno-venous bypass is used, hemostatic techniques can be applied so that most, if not all, bleeding can be controlled. Moreover, the use of a venous bypass system results in improved intraoperative cardiovascular stability, preservation of renal function by avoidance of renal vein hypertension, excessive blood loss, trauma to the gastrointestinal tract, and the creation of an operating room ambience compatible with training.

## Operative Problems

### Inadequate Recipient Artery

Hepatic transplant surgeons must be ready to use arterial grafts if the recipient's hepatic artery is either too small or too inconveniently located to permit an adequate anastomosis. The easiest solution to such problems is to attach the homograft's hepatic artery to the recipient's abdominal aorta inferior to the origin of the renal arteries. The extra length of the vessel required to reach this location can be obtained by using as a graft either the thoracic aorta of the donor, in continuity with the celiac axis and by turning the donor aorta 180°, or the donor common iliac artery after ligating the hypogastric artery. Fortunately, the external iliac artery is almost always a perfect match with the graft's celiac axis.

### Portal Vein Problems

If portal venous thrombosis, sclerosis, or hypoplasia is present and involves the splenic and inferior mesenteric veins, the confluence of these veins must be dissected free from the pancreas. A cloaca can be created at this junction to which an iliac vein graft can be anastomosed to provide the added length required to reach the donor's portal vein. Without such grafts, many patients with portal vein problems, particularly portal vein thrombosis, die in the operating room.

### Biliary Tract Reconstruction

Most of the technical complications experienced in the early days of liver transplantation were associated with biliary tract reconstruction (61,62). Worse yet, these problems were often not recognized until quite late in the postoperative course. As a result, they were associated with abscess formation and other forms of sepsis that contributed directly to the death of patients. Primarily because of its convenience, early in clinical liver transplantation a cholecystoduodenostomy was used as the biliary anastomosis. The prevalence of bacteremia following this type of biliary drainage procedure was considerable. The organisms usually recovered were those indigenous to the gastrointestinal tract (61,62). This situation with the biliary anastomosis was improved somewhat with the use of a defunctionalized jejunal limb (Roux-en-Y) to which the gallbladder was anastomosed. However, because of frequent cystic duct obstruction (in more than one-third of the recipients with this type of biliary anastomosis), this method of biliary drainage frequently required one or more surgical revisions and, ultimately, conversion to a choledochojejunostomy. Current practice is to create a choledochocholedocho anastomosis unless prior biliary tract surgery has been accomplished, in which case a choledochojejunostomy (Roux-en-Y) is created. The duct-to-duct anastomosis is performed with interrupted absorbable sutures, using a T-tube stent whenever possible. The T-limb is brought out through a choledochotomy in the recipient's portion of the composite duct. In small children and occasionally in adults, the available T-tubes are too large for such drainage and an internal stent is required, with the distal tip being passed into the duodenum. During the graft procedure, the homograft common

duct must be cut high so that its distal end is well arterialized from the liver. Anatomic studies have shown that the blood supply to the graft's bile duct is dependent upon retrograde perfusion from hilar vessels and late intra- and extrahepatic biliary strictures are common if this blood supply is not adequate (61,62).

### Other Operative Problems

Coagulation defects must be anticipated in all cases. The bleeding experienced intraoperatively can be aggravated by fibrinolysis, which often begins just before the revascularization of the homograft. At times, bleeding can assume crisis proportions. This circumstance may represent a unique manifestation of the hyperacute rejection process seen in liver transplantation. In such cases, bleeding control starts with suture ligation and cautery. With the new liver in place, the portal system can be decompressed through the new organ, with the elimination of portal hypertension as an additional contributing factor in controlling the bleeding. Meanwhile, platelets, fresh frozen plasma, and blood constituents should be transfused as necessary. The most common early postoperative difficulties include pulmonary insufficiency, renal failure, and persistent intra-abdominal bleeding.

### Late Postoperative Problems

#### Major Problems

The list of late complications includes peritonitis, with or without bowel infarction, bile leaks and/or obstruction pancreatitis, pulmonary emboli, extra-abdominal infections, and psychosis. The most important factor in recipient survival is the ability to control graft rejection. Azathioprine and prednisone have been shown to have synergistic effects as immunosuppressant agents when given together. This combination was the most commonly used immunosuppressive regimen worldwide until recently, when cyclosporine became available (63-74). Currently, the combination of cyclosporine and steroids is used most frequently. Adjuvants to this combination include antilymphocyte or antithymocyte globulins (ALG or ATG) and, more recently, monoclonal antithymocyte globulin (OKT<sub>3</sub>), which are given intravenously with standard immunosuppressive agents during the first few weeks or months after transplantation when rejection cannot be controlled by other means.

Nephrotoxicity is the most serious side effect of cyclosporine use (73,74). Fortunately, the renal dysfunction seen with cyclosporine can be reversed with appropriate reduction of the dose. Gum hyperplasia, a fine tremor, regional flushing, vague abdominal discomfort, seizures, and the development of breast fibroadenomas are other known side effects. Although hepatotoxicity has been reported, this untoward effect of cyclosporine has rarely been serious in liver transplant recipients and can be controlled by dose reduction when it occurs (74).

The most disturbing consequence of cyclosporine use has been the development of an Epstein-Barr virus (EBV)-related lymphoproliferative syndrome and lymphoma (75). In contrast, the risk of de novo epithelial malignancies with

cyclosporine may be less than that experienced with previously used conventional immunosuppressive regimens and, as yet, no such tumors have been reported in cyclosporine-treated patients. With previously used conventional immunosuppressive drugs, epithelial tumors accounted for 75% of the new tumors seen (75).

Cyclosporine is usually started preoperatively with an oral dose of 17.5 mg/kg. It is continued daily thereafter, but with reduced intravenous (IV) doses, and is given twice a day until oral intake can be resumed. At this time, an oral dose of 17.5 mg/kg/day is gradually substituted for the IV dose and is typically divided into a twice-daily dosage schedule. Steroids are started on the day of operation. For adult patients who leave the operating room in relatively good condition, a 5-day burst of prednisolone is given, starting at a dose of 200 mg and declining by 40 mg/day until a maintenance dose of 20 mg/day is achieved.

If the patient is in poor condition, the initial burst of high-dose steroid therapy can be omitted and replaced with an infusion of OKT<sub>3</sub>. A few patients suspected of having cyclosporine nephrotoxicity have been switched temporarily to azathioprine, with resumption of cyclosporine treatment after improvement in their renal function. With less severe renal impairment, the dosage of cyclosporine is simply reduced, without the addition of azathioprine.

If rejection occurs, the principal response has been to administer intermittent large doses of methylprednisolone IV, or to repeat the original 5-day burst of steroids, or to settle at a higher maintenance level of steroids. Most recently, OKT<sub>3</sub> has been used for 7–10 days in such cases.

Histopathologically, the first sign of rejection in human recipients is the appearance within the liver of lymphoblastoid cells that appear to leave the smallest portal vessels throughout the graft and accumulate in the portal tracts beneath the endothelial lining of the sinusoids. Due to this cellular infiltration, the sinusoids become progressively narrowed and occasionally occluded. As a result, blood flow through the liver can decrease, with the development of centrilobular ischemia and occasional necrosis (76–78). In severe cases this centrilobular necrosis can progress to midzonal necrosis, and biochemical liver function rapidly deteriorates.

Marked centrilobular cholestasis and canalicular cholestasis can also occur. A precise pathophysiologic explanation for this cholestasis has not yet been established. With chronic rejection, the intralobular bile ducts vanish (77–78). Fibrosis develops and can progress to a true portal cirrhosis in some cases. A characteristic feature of the chronic rejection process is intimal and subintimal vascular thickening. Hepatic blood flow is reduced in cases of severe rejection, making the ischemic liver graft unusually susceptible to bacterial invasion (79–81).

Currently, the clinical diagnosis of chronic rejection is restricted to those patients whose graft biopsy specimens demonstrate arterial intimal thickening, hepatic fibrosis, or bile duct paucity. The morphologic findings of chronic rejection are not related directly to the postoperative interval and can be seen within the first few postoperative months. The clinical manifestations of chronic rejection are similar to those of chronic liver failure due to any cause. In contrast to the process of acute hepatic rejection, chronic rejection does not respond to increased immunosuppression.



## Causes of Posttransplantation Mortality

The greatest mortality experienced after liver transplantation occurs early, usually within the first few months following the procedure. This is true both with liver transplantation under conventional immunosuppression and with cyclosporine-steroid regimens. Detailed analyses of the causes of this early mortality have been published. The causes of graft failure include primary graft failure, massive operative hemorrhage, vascular thrombosis of one of the reconstituted homograft blood vessels, intraoperative cerebral air embolism, the presence of unanticipated recipient abnormalities, anatomic situations created by previous operations, preexisting disabilities, defective biliary tract reconstructions, and excessive immunosuppression (especially with prednisone).

The dominant pathologic diagnoses in grafts that fail are rejection, biliary obstruction, recurrent carcinoma, HBV infection, and recurrent Budd-Chiari syndrome which occurs less often (77,78). The time at which changes in current postoperative management are most likely to produce a substantial reduction in future mortality figures is during the immediate perioperative period.

The effect of the original disease indication for liver transplantation and the technical difficulty of the procedure have not been recognized as being important until relatively recently. Clearly, when patients with previous abdominal operations at or near the hepatic hilum (such as repeated biliary tract reconstructions and/or portacaval anastomosis) undergo liver transplantation, the procedure is considerably more difficult. As a result, survival in such cases is reduced. In this regard, it is important to remember that surgical procedures that jeopardize the candidacy for transplantation should be avoided in patients with chronic liver disease. Fortunately, alternative procedures utilizing interventional radiologic techniques are becoming more widely available. Moreover, sclerotherapy for the control of variceal bleeding rather than portal diversion is becoming increasingly accepted as a reasonable therapy.

## Retransplantation

When a transplanted liver fails, aggressive attempts at retransplantation offer the only chance for survival. One of the more commonly seen judgment errors in liver transplantation is the attempt to gain improvement in hepatic function with greater and greater degrees of immunosuppression until the chance for retransplantation is lost as a result of sepsis. Retransplantation, when performed early, is surprisingly easy to do. The procedure is greatly simplified by retaining vascular cuffs from the supra- and infrahepatic venae cavae and from the portal vein of the failing graft. Total retransplantation operative time can be as little as 3–4 hours.

## Factors That Affect Survival

Certain risk factors have been examined for their effect on survival. Among the more important ones is age. Throughout the entire history of liver transplantation, pediatric recipients have fared better by 10%–25% than have adults. Two high-risk diseases have been identified. Specifically, survival with postnecrotic cirrhosis and with primary hepatic tumors is less than it is for any other indi-

cation. With cirrhosis, the principal problems are the numerous surgical difficulties caused by the pathologic process (coagulopathy and portal hypertension), the poor condition of the cirrhotic patient, and the universal return of the original B virus-induced disease in HBV carriers. In patients with primary hepatic malignancy the early mortality is low, with more than 80% of the recipients alive at 6 months. Unfortunately, a steady decline occurs thereafter as a result of recurrent tumor.

## The Future

The future of liver transplantation is bright. Clearly, as a result of increasing experience, concept development and the formation of principles of disease development, progression, and therapy are to be expected. Currently, it is generally held that specific liver diseases require specific therapies. In the future, subtypes of various complications of liver disease such as hepatic encephalopathy will require specific and different therapeutic modalities. Crisis management in the field of liver disease has been and will continue to be replaced by carefully thought-out and selected therapies that will be initiated not in response to but in an effort to prevent the development of a complication of liver disease.

Such developments should lead to fewer transplants being performed for end-stage liver disease and more being performed for selected indications. As the clinical arena of liver disease shifts from crisis management to disease control and the application of specific therapies for specific indications, one or more artificial livers, which perform one or more hepatic functions, will be developed. As a result, liver transplantation for fulminant hepatic failure will be utilized less often, but will be applied more often for the problem of subacute hepatic failure.

It should be noted that liver transplantation provides hepatologists not only with challenges but also with the tools to address these new challenges. Specifically, liver transplantation centers will become centers of excellence in hepatic disease in its broadest sense. As a result, patients with liver disease will either seek out or be referred to such centers. Thus the epidemiology and natural history of poorly defined and as yet unrecognized liver diseases will be identified throughout the entire course of the disease. The removed organs will provide tissues, cells, viruses, DNA and other materials, and agents that are responsible for or which modify the liver disease.

Patients with new organs and on immunosuppressive therapy will develop old diseases with new faces, as well as totally new diseases. Issues relative to the complications, progression, and/or reversal of hepatic disease following liver transplantation will be addressed. The important issue of disease recurrence in a new organ will be considered. The forces that produce these diseases or modify their presentation, when and if they recur, will be identified and studied. The information gained will provide new insights into the pathogenesis of individual liver diseases and their complications.

Thus, hepatologists will be challenged to:

1. develop better definitions of diseases.
2. identify specific disease mechanisms.

3. clarify the pathophysiologic mechanisms of hepatic disease complications involving other organs, such as the brain, bone, lungs, kidneys, and endocrine systems.

Concerning the specific issue of disease recurrence, we already know that certain diseases, such as the Budd-Chiari syndrome, hepatic cancer, and cholangiolar cancer, as well as HBV-positive (DNA + ) disease, recur in the allograft. Does NANB hepatic disease recur as well? Do primary biliary cirrhosis and primary sclerosing cholangitis recur? Does autoimmune chronic active hepatitis recur? To the naive, these questions appear rather simple and easy to answer, but to the committed hepatologist and transplant surgeon, they are currently very difficult, if not impossible, to answer. The reason for this marked difference in perspective is that the latter two types of physicians recognize the problems of specific liver disease identification based upon present standards (44). Currently, only a few liver diseases are diagnosed utilizing the identification of a specific agent or enzyme defect and the characteristic histopathology and/or clinical course. These diseases can be said to be identified utilizing a "gold standard." Many more liver diseases are recognized as a result of a "silver standard" that involves a characteristic and unique but not pathognomonic pathology, often with characteristic and unique serologic responses. Unfortunately, no specific agent or pathophysiologic mechanism of disease has been recognized in these cases. Even more discouraging, however, is the fact that many more liver diseases are identified utilizing a "copper standard." That is, they have a characteristic but not unique pathology, and no characteristic serologic or biochemical markers. Clearly, utilizing anything but a gold standard makes the recognition of disease recurrence, as distinct from the development of a new disease in a new organ, difficult, if not impossible.

Additional questions that will be answered as a result of the increasing experience with liver transplantation include the following:

1. Why do liver rejection and chronic active hepatitis differ so markedly histopathologically when the mechanisms involved appear to be so similar, and dependent upon an active T-cell-dependent immune response?
2. What is the role of cell surface and intracellular organelle antigens in liver disease initiation, progression, perpetuation, and possibly disease recurrence?

It is expected that new and better methods of rejection control and, hopefully, prevention (tolerance) will be developed. These will include methods or techniques of modulating antigen processing cell (APC cells) and suppressor cell numbers, function, and lymphokine modulation/neutralization.

An alternative to enhanced prevention or control of rejection will be methods and techniques of initiating, modulating, and selectively regulating hepatocyte and bile duct cell regeneration. Should controlled regeneration be possible, at a rate that equals the rate of losses due to rejection, a new and entirely different state of or concept of "tolerance" will develop.

The knowledge that evolves from attempts to achieve these aims in the clinical arena of liver transplantation will also be applied to the problem of fulminant hepatic failure. Growth factors or regeneration modulators will be developed and used in patients with this lethal problem. As a result, the number of transplanations for fulminant hepatic failure will be reduced, and the number

of such patients recovering without the need for transplantation (new successes), as well as the number operated on for subacute hepatic failure (persistent therapy failure), will increase. Fortunately, the number of the latter will be reduced markedly from the current level.

Finally, the organs removed at the time of transplantation will provide the necessary raw materials for the preparation, characterization, and probable *ex vivo* production of somatomedins and osteocalcins, materials that can be used to treat and/or prevent the growth failure and bone disease that currently characterize patients with advanced liver disease.

Clearly, much has been learned from the past. Much continues to be done. And the future is very promising.

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